



Original Article

Association between glaucoma and sleep apnea in a large French multicenter prospective cohort



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ABSTRACT

Objective: Several reports suggest that glaucoma may be linked to obstructive sleep apnea (OSA). Herein, we investigated this hypothesis in the largest reported sample to date.

Methods: Data were from the French multicenter prospective cohort study including OSA-suspected patients from private practice, general and teaching hospitals. Demographics, history, comorbidities and sleep studies from patients aged >50 years were analyzed. Univariate and multivariate logistic regression were used to predict the odds ratio of prevalent glaucoma depending on sleep apnea status and other potential anthropometric, metabolic, cardiovascular and respiratory confounders.

Results: A total of 9580 patients aged >50 years were included. Among these patients, 6754 had sleep apnea and 330 had glaucoma. Glaucoma prevalence was 3.55% in patients with OSA and 3.14% in patients without OSA. OSA diagnosis did not significantly influence the risk of glaucoma in univariate analysis (odds ratio [OR], 1.13; 95% confidence interval [CI], 0.87–1.47). The variables significantly influencing the odds of glaucoma with multivariate regression were age >61.4 years (OR, 1.55; 95% CI, 1.23–1.95), body mass index <30 kg/m² (OR, 1.58; 95% CI, 1.26–1.99), female gender (OR, 1.40; 95% CI, 1.11–1.78), arterial hypertension (OR, 1.32; 95% CI, 1.05–1.67), high triglyceride levels (OR, 2.03; 95% CI, 1.43–2.88) and thyroid dysfunction (OR, 1.52; 95% CI, 1.09–2.11).

Conclusions: When confounders are taken into account, patients with OSA do not have higher odds of glaucoma compared with patients who do not have OSA in a large multicenter prospective cohort.

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1. Introduction

Obstructive sleep apnea (OSA) is a common medical condition characterized by repetitive partial or complete obstruction of the upper airway causing repetitive nocturnal oxygen desaturation, i.e., chronic intermittent hypoxia [1–3]. Intermittent hypoxia induces oxidative stress and consequently promotes systemic and vascular inflammation, insulin resistance, endothelial dysfunction, and cardiovascular morbidity and mortality.

A significant association between OSA and glaucoma continues to be debated [4–20]. Most of the studies conducted to address this

issue are case series or cross-sectional studies with limited sample sizes in which glaucoma screening was performed only in OSA patients without a control group free of the disease. Most of these studies concluded in a positive association between glaucoma and OSA [4–8,10–13,17]. Only two case–control studies evaluated the prevalence of glaucoma using a large number of OSA patients and controls [18,19]. These two studies did not conclude in a significant association between OSA and glaucoma. One concern about these two studies could be that the severity of OSA was unknown and ‘controls’ were not systematically assessed for sleep apnea by sleep studies.

Taking advantage of a large multicenter, clinical cohort including patients investigated for suspected OSA in private practice, general hospitals and teaching hospitals in France in which

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patients underwent sleep studies to characterize OSA, we evaluated the prevalence of glaucoma in patients with and without OSA and assessed whether OSA increased the risk of glaucoma independently of other potentially confounding demographic, anthropometric, metabolic and cardiovascular factors.

2. Methods

2.1. Data source

The research database of the Observatoire Sommeil de la Fédération Française de Pneumologie (OSFP) is a large, high-quality, not-for-profit prospective multicenter clinical cohort administered by the French Federation of Pneumology. The database contains de-identified longitudinal medical records from more than 500 respiratory physicians in private practice, general hospitals and university hospitals (<http://www.osfp.fr>). This registry is a formatted web-based report, prospectively collecting data from patients complaining about disturbed sleep, completed and validated by respiratory physicians. Participating physicians are trained in the use of computerized medical records and appropriate software. Periodic quality control checks are performed to ensure up-to-standard data recording. Data collection was started in January 2009, and data extraction for analysis was performed in May 2012.

The database contains detailed records of patients' demographic, socioeconomic and clinical characteristics as well as medication intake [21]. Medical information includes ocular and non-ocular conditions. Metabolic, cardiovascular and respiratory comorbidities are exhaustively detailed. Anthropometric items include the patient's height, weight, body mass index (BMI: kg/m²), waist circumference, physical activity, cholesterol and triglyceride levels, blood glucose levels, and tobacco consumption. Cardiovascular and respiratory information includes systolic and diastolic blood pressure, arterial blood gas (PaO₂, PaCO₂, pH), pulmonary function test, data from sleep studies (including the apnea–hypopnea index and the percentage of time at night with oxygen saturation <90%), and subjective sleepiness (Epworth sleepiness scale).

Ethics committee approval was obtained from Le Comité consultatif sur le traitement de l'information en matière de recherche en santé (CCTIRS no. 09.521) and authorization from the Commission Nationale Informatique et Liberté (CNIL), the French information technology and personal data protection authority. The OSFP Independent Scientific Advisory Committee approved data use for this study.

2.2. Population studied

Owing to the age-related prevalence of glaucoma, we included all subjects in the database aged ≥50 years, with metabolic, cardiovascular and respiratory data available, as well as the apnea–hypopnea index and the percentage of time at night with oxygen saturation <90%. Glaucoma diagnosis was collected in the database only for patients who have been examined by an ophthalmologist.

2.3. Statistical analysis

Descriptive statistics were performed, with quantitative variables expressed by mean ± SD, median (interquartile range), range, and qualitative variables expressed as percentages. The number of missing data was calculated for continuous and qualitative variables. Variables with >15% missing data were not addressed in future analyses.

The SAS software version 9.1.3 Service Pack 4 (SAS Institute, Cary, NC, USA) was used to perform data analysis. The primary goal

of the study was to evaluate the prevalence of glaucoma (diagnosis of glaucoma in the patients' medical records) in patients with sleep apnea (diagnosis of sleep apnea confirmed by respiratory polygraphy or polysomnography data) or without sleep apnea. The influence of OSA on glaucoma prevalence was estimated using multivariable logistic regression models and expressed as the odds ratio (OR) with 95% confidence intervals. Obstructive sleep apnea was defined as an apnea–hypopnea index (AHI) ≥ 15/h. Potential confounders that were included in the multivariate analysis included age, sex, height, weight, body mass index, arterial hypertension, tobacco consumption, high cholesterol levels, high triglyceride levels, and thyroid dysfunction. The influence of OSA severity on glaucoma prevalence was estimated by calculating the prevalence of glaucoma in the control group (AHI < 15/h) and in the OSA subgroups (AHI 15–30, 30–50, and >50/h). Statistical significance was set at $P \leq 0.05$.

3. Results

3.1. Population characteristics

Among the 9580 patients in the database who met the inclusion criteria, 6754 had sleep apnea and 330 had glaucoma. The subjects'

Table 1

Demographic and medical characteristics of patients included (N = 9580).

Data variables	Mean ± SD or %	Median (Q1; Q3)
<i>Demographic data</i>		
Age (years)	63.25 ± 8.76	61.82 (56.23; 69.15)
BMI (kg/m ²)	30.86 ± 6.31	30.02 (26.51; 34.21)
Waist circumference (cm)	107.28 ± 15.62	107.00 (97.00; 117.00)
AHI (number/h)	29.74 ± 22.09	27.00 (11.00; 43.00)
Sex (% male)	68.00%	
<i>Medical history</i>		
COPD (%)	7.20%	
Chronic respiratory failure (%)	2.00%	
Hypertension (%)	52.20%	
Myocardial infarction (%)	5.00%	
Angina pectoris (%)	7.70%	
Arrhythmias (%)	11.10%	
Stroke (%)	4.30%	
Heart failure (%)	4.30%	
Peripheral vascular disease (%)	3.20%	
Current tobacco consumption (%)	12.00%	
Current alcohol consumption (%)	4.60%	
Diabetes (%)	18.70%	
High cholesterol levels (%)	33.70%	
High triglyceride levels (%)	6.40%	
Thyroid dysfunction (%)	8.90%	
OSA (%)	74.14%	
<i>Blood pressure data</i>		
Systolic BP (mmHg)	135.45 ± 15.90	130.00 (127.00; 140.00)
Diastolic BP (mmHg)	79.07 ± 10.71	80.00 (70.00; 84.00)
<i>Biological parameters</i>		
Fasting glucose (g/L)	1.12 ± 0.43	1.02 (0.92; 1.16)
Cholesterol levels (g/L)	2.02 ± 0.54	1.97 (1.68; 2.30)
HDL cholesterol (g/L)	0.55 ± 0.39	0.48 (0.41; 0.59)
LDL cholesterol (g/L)	1.24 ± 0.43	1.20 (0.95; 1.48)
Triglyceride levels (g/L)	1.46 ± 0.98	1.21 (0.88; 1.68)
<i>Pulmonary function tests</i>		
FEV1 (%)	92.18 ± 22.56	94.00 (80.00; 107.00)
FEV1/FVC (%)	87.15 ± 17.21	83.00 (76.00; 99.00)
TLC (%)	66.81 ± 36.56	48.60 (39.00; 97.00)

Q1, first quartile; Q3, third quartile; BMI, body mass index; AHI, apnea–hypopnea index; COPD, chronic obstructive pulmonary disease; SAS, sleep apnea syndrome; OSA, obstructive sleep apnea; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FEV1, forced expiratory volume in 1 s; FEV1/FVC, forced expiratory volume in 1 s/forced vital capacity ratio; TLC, total lung capacity.

Table 2Demographic and medical characteristics of patients with and without obstructive sleep apnea ($N = 9580$).

Data variables	Patients with OSA AHI ≥ 15 ($n = 6754$)	Patients without OSA AHI < 15 ($n = 2826$)	P-value
Demographic data			
Age (years)	62.43 (56.89; 69.91)	60.37 (55.17; 67.27)	<0.0001
Height (cm)	170.00 (163.00; 175.00)	168.00 (160.00; 174.00)	<0.0001
Weight (kg)	88.00 (78.00; 100.00)	81.00 (70.00; 93.00)	<0.0001
BMI (kg/m^2)	30.65 (27.14; 34.89)	28.58 (24.98; 32.53)	<0.0001
Waist circumference (cm)	108.00 (99.00; 119.00)	102.00 (92.00; 113.00)	<0.0001
AHI (number/h)	35.00 (25.00; 51.00)	7.00 (3.00; 10.00)	<0.0001
Sex (% men)	72.32%	58.14%	<0.0001
Medical history			
COPD (%)	6.85%	8.07%	0.0460
Chronic respiratory failure (%)	2.05%	1.80%	0.5048
Arterial hypertension (%)	55.88%	43.90%	<0.0001
Myocardial infarction (%)	5.75%	3.42%	<0.0001
Angina pectoris (%)	8.52%	5.69%	<0.0001
Arrhythmias (%)	11.72%	9.76%	0.0049
Stroke (%)	4.60%	3.63%	0.0302
Heart failure (%)	4.83%	3.19%	0.0003
Peripheral vascular disease (%)	3.41%	2.78%	0.2050
Current tobacco consumption (%)	11.44%	13.26%	0.0114
Current alcohol consumption (%)	5.25%	3.15%	<0.0001
Diabetes (%)	20.74%	14.00%	<0.0001
High cholesterol levels (%)	36.41%	27.49%	<0.0001
High triglyceride levels (%)	7.32%	4.24%	<0.0001
Thyroid dysfunction (%)	8.32%	10.22%	0.0026
Blood pressure data			
Systolic BP (mmHg)	135.00 (130.00; 142.00)	130.00 (120.00; 140.00)	<0.0001
Diastolic BP (mmHg)	80.00 (70.00; 85.00)	80.00 (70.00; 80.00)	<0.0001
Biological parameters			
Fasting glucose (g/L)	1.03 (0.93; 1.16)	1.00 (0.90; 1.12)	0.0478
Cholesterol levels (g/L)	1.96 (1.69; 2.29)	2.01 (1.66; 2.33)	0.5942
HDL cholesterol (g/L)	0.47 (0.40; 0.58)	0.52 (0.43; 0.62)	0.0057
LDL cholesterol (g/L)	1.20 (0.97; 1.48)	1.22 (0.93; 1.48)	0.9924
Triglycerides levels (g/L)	1.22 (0.90; 1.74)	1.14 (0.84; 1.60)	0.0556

OSA, obstructive sleep apnea; AHI, apnea–hypopnea index; BMI, body mass index; COPD, chronic obstructive pulmonary disease; SAS, sleep apnea syndrome; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Data are presented with median, first quartile and third quartile.

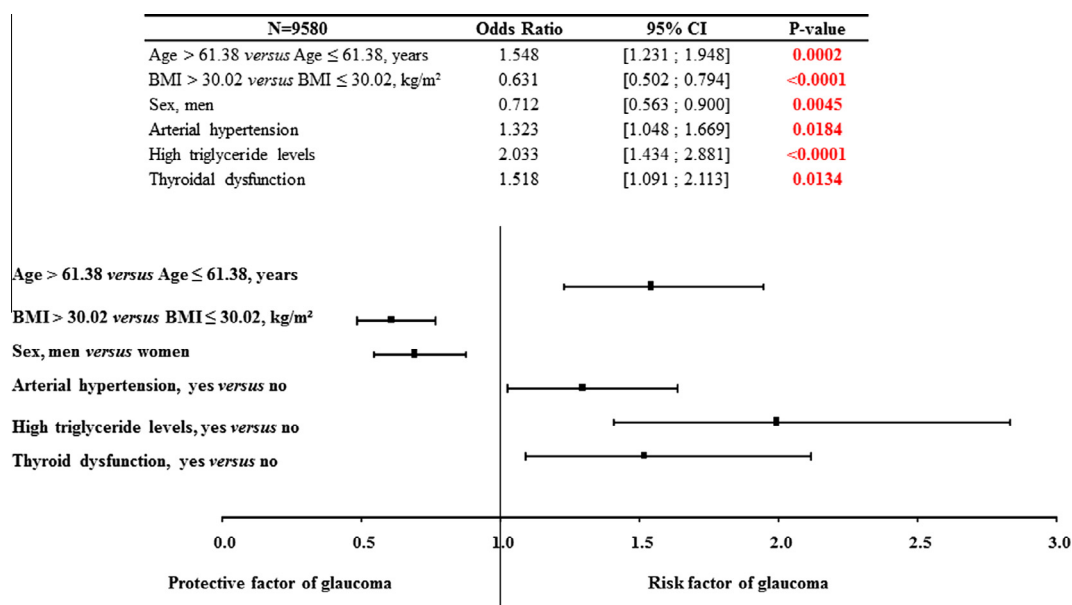


Fig. 1. Variables significantly influencing the odds ratios of glaucoma with multivariate logistic regression. CI, 95% confidence interval; BMI, body mass index.

characteristics are described in Table 1. Glaucoma prevalence was 3.55% in patients with OSA and 3.14% in patients without OSA ($P = 0.22$). The characteristics of patients with and without OSA are described in Table 2.

3.2. Univariate and multivariate logistic regression

The results of the univariate and multivariate logistic regressions are shown in Table 2 and Fig. 1. The variables significantly

Table 3
Univariate logistic regression.

Data variables	Patients with glaucoma (n = 330)	Patients without glaucoma (n = 9250)	OR	95% CI	P-value
<i>Demographic data</i>					
Age > 61.38 versus age ≤ 61.38 (years)	65.34 ± 8.50	63.18 ± 8.76	1.646	1.313; 2.063	<0.0001
BMI > 30.02 versus BMI ≤ 30.02 (kg/m ²)	29.36 ± 6.13	30.92 ± 6.31	0.721	0.577; 0.901	0.0040
Sex (% male)	59.7	68.2	0.689	0.551; 0.862	0.0011
<i>Medical records</i>					
COPD (%)	6.4	7.3	0.885	0.565; 1.388	0.5953
Chronic respiratory failure (%)	1.5	2.0	0.759	0.310; 1.858	0.5459
Hypertension (%)	59.4	51.9	1.354	1.083; 1.693	0.0079
Myocardial infarction (%)	4.8	5.0	0.961	0.577; 1.602	0.8791
Angina pectoris (%)	7.0	7.7	0.901	0.586; 1.386	0.6356
Arrhythmias (%)	13.0	11.0	1.206	0.870; 1.673	0.2609
Stroke (%)	5.2	4.3	1.218	0.740; 2.004	0.4385
Heart failure (%)	3.9	4.3	0.905	0.515; 1.590	0.7284
Peripheral vascular disease (%)	2.4	3.2	0.741	0.364; 1.509	0.4088
Tobacco consumption (%)	8.2	12.1	0.645	0.433; 0.961	0.0312
Alcohol consumption (%)	3.9	4.6	0.844	0.481; 1.483	0.5563
Diabetes (%)	19.4	18.7	1.050	0.796; 1.387	0.7291
High cholesterol levels (%)	40.3	33.4	1.345	1.075; 1.683	0.0096
High triglyceride levels (%)	11.8	6.2	2.038	1.443; 2.876	<0.0001
Thyroid dysfunction (%)	14.2	8.7	1.740	1.267; 2.389	0.0006
OSA (%)	76.4	74.1	1.131	0.874; 1.465	0.3490

OR, odds ratio; CI, confidence interval; BMI, body mass index; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea.

influencing the risk of glaucoma with univariate logistic regression were age >61.38 years versus age <61.38 years (odds ratio [OR], 1.65; 95% confidence interval [CI], 1.31–2.01), BMI > 30 versus BMI < 30 (OR, 0.72; 95% CI, 0.58–0.90), hypertension (OR 1.35; 95% CI, 1.08–1.69), tobacco consumption (OR, 0.64; 95% CI, 0.43–0.96), high cholesterol levels (OR, 1.34; 95% CI, 1.07–1.68), high triglyceride levels (OR, 2.04; OR, 1.44–2.87) and thyroid dysfunction (OR, 1.74; 95% CI, 1.27–2.39). OSA diagnosis did not significantly influence the risk of glaucoma in univariate analysis (OR, 1.13; 95% CI, 0.87–1.47, respectively). The significant variables in univariate analysis were then entered in the multivariate analysis. The variables significantly influencing the odds of glaucoma with multivariate regression were age >61.38 years versus age <61.38 years (OR, 1.55; 95% CI, 1.23–1.95), BMI > 30 versus <30 (OR, 0.63; 95% CI, 0.50–0.79), gender with a lower risk in men (OR, 0.71; 95% CI, 0.56–0.90), hypertension (OR, 1.32; 95% CI, 1.05–1.67), high triglyceride levels (OR, 2.03; OR, 1.43–2.88) and thyroid dysfunction (OR, 1.52; 95% CI, 1.09–2.11).

3.3. Influence of OSA severity on glaucoma prevalence

The prevalence of glaucoma was 3.14% in patients without OSA, and 4.95% in OSA patients with AHI 15–30/h, 3.79% in OSA patients with AHI 30–50/h, and 3.14% in OSA patients with AHI > 50/h. There was no significant dose–response relationship between OSA severity and glaucoma prevalence (Table 3).

4. Discussion

4.1. Summary of the main results

Using a large national multicenter prospective clinical cohort, we investigated the prevalence of glaucoma in patients with and without OSA objectively characterized by sleep studies. In both univariate and multivariate analysis, we found that neither obstructive sleep apnea diagnosis nor severity of OSA significantly increased the risk of glaucoma. In multivariate analysis, we found that age, female gender, lower BMI, systemic hypertension, high triglyceride levels, and thyroid dysfunction had a significant impact on glaucoma risk.

4.2. What the study adds to the field

We conducted a literature search in the PubMed database of studies published up to May 30, 2013, using the following search terms: ‘glaucoma’, ‘ocular hypertension’, ‘optic nerve’, ‘retinal nerve fiber layer’, and ‘sleep apnea.’ Seventeen studies were found [4–20]. Eleven studies concluded in a positive association between glaucoma and OSA [4–8,10–13,17–20], whereas the remaining six provided contrary conclusions [9,14–16,18,19]. The majority of these studies suffer from several limitations. Some included a small sample, leading to discrepancies in the results. About half of these studies did not include a control group without OSA. Finally, the diagnosis of OSA in some of these studies was based on the patient’s symptoms and/or physician-administered questionnaires, but not on a sleep study.

The last three studies identified were database-based case-control studies including a large number of patients and controls [18–20]. Two of these studies were conducted in the USA, the first using computerized data files from a veterans’ medical center and the second using a large database collecting longitudinal medical records from patients in all 50 US states [18,19]. These two well-designed studies did not conclude in a significant association between OSA and glaucoma. These two studies have many similarities with our study, particularly the second, which is a large national database study evaluating the prevalence of glaucoma in subjects with and without OSA that also analyzes the effect of several potentially confounding cardiovascular and metabolic factors. The present study also differs from the two above-mentioned studies, making the comparable results noteworthy. Our study enrolled patients from all regions in France, whereas the two previous database-based studies were conducted in the USA. American and French populations could have different characteristics – for example, in terms of ethnic origin – that could lead to differences in prevalence of glaucoma, or in terms of biometric characteristics that could lead to differences in prevalence of OSA or related conditions (obesity, cardiovascular events, diabetes, etc.) [22,23]. Another difference is that we had access to sleep study data, making it possible to assess not only OSA diagnosis, but also a potential dose–response relationship between the severity of OSA and glaucoma. This is a major strength in this study since this relationship should be demonstrated to validate a risk factor [24]. In contrast, the diagnosis of OSA in the two other above-mentioned studies

was made using disease classification diagnosis codes or billing codes, possibly introducing errors such as miscoding, misdiagnosis, diagnosis of OSA made by physicians without overnight polysomnography, or diagnosis of OSA based on criteria differing from commonly accepted criteria.

The third database-based case–control study, conducted in Taiwan, did not evaluate the relationship between glaucoma prevalence and OSA, but retrospectively evaluated the incidence of glaucoma during a five-year period after a diagnosis of OSA in subjects without glaucoma, finding an increased risk compared to controls [20].

4.3. Limitations of the study

The present study has several limitations. From the database, we know the glaucoma status but do not have other information on the eye status (refractive status, intraocular pressure, visual fields, optic nerve head examinations, etc.). First, some of these parameters are well-identified risk factors of glaucoma and should have been included as potential confounding factors in the univariate and multivariate analysis, particularly intraocular pressure given that this parameter has been demonstrated to be influenced by OSA or its treatment (continuous positive pressure) [25–27]. Second, the lack of ocular data makes it impossible to strictly check the diagnosis of glaucoma. In order to prevent misdiagnosis of glaucoma, glaucoma diagnosis was collected in the database only for patients who have been examined by an ophthalmologist. Moreover, we have full access to all systemic and topical medications taken by patients, and have used this information to check the diagnosis of glaucoma. In order to evaluate whether misdiagnosis could have biased the results of the study, we have performed a second similar analysis comparing patients with glaucoma and having glaucoma hypotensive eye drops versus patients without glaucoma and not having glaucoma hypotensive eye drops. We found similar results when performing the second analysis: OSA diagnosis did not significantly influence the risk of glaucoma in univariate analysis (OR, 1.09; 95% CI, 0.76–1.58; $P = 0.64$).

Another limitation of the present study is that the database included patients complaining about sleep recruited by respiratory specialists, potentially inducing a selection bias from referral mechanisms, particularly for the group of patients without OSA. As we have evaluated and compared the prevalence of glaucoma in a group of patients complaining about disturbed sleep and having OSA, and a group of patients complaining about sleep and not having OSA, the second group cannot be formally considered as a group of controls.

4.4. Strengths of the study

The large sample size of the database allows analyzing the data of a large number of subjects with glaucoma, OSA, and the potentially confounding factors. We included a much higher number of subjects with OSA than the previous studies, except the study reported by Stein et al. [19]. We used a national database, enrolling patients throughout the country – thus reducing the risk of private practice and hospital selection bias – completed by more than 500 physicians, thus reducing the risk of observer bias. Analyses of administrative data also reduce the risk of attention or expectation bias that may lead to overestimation of disease prevalence in such studies.

One particular strength of the study is that data were collected by respiratory specialists, reducing the risk of OSA misdiagnosis. Moreover, we only included patients for whom polysomnography results were available in the database. This strictly confirms the presence or absence of OSA and is more accurate than database studies in which OSA was identified only with disease classification

billing codes. In those studies, the diagnosis of SAS is based on the judgments of the physician who coded the diagnosis (OSA diagnosis criteria may vary among doctors; OSA diagnosis could have been based on patient's subjective symptoms and without overnight polysomnography; etc.). Polysomnographic data can also be used to evaluate the influence of sleep apnea severity, whereas this was not done in previous database-based studies. Moreover, the database used in the present study focuses on sleep apnea and therefore included a great deal of information on related metabolic and cardiovascular conditions, allowing careful evaluation of their effect as potential confounding factors.

5. Conclusions

In a database of patients undergoing overnight polysomnography, patients who had obstructive sleep apnea do not have higher odds of glaucoma compared with patients who do not have obstructive sleep apnea. The results of the present study therefore do not support the recommendation of conducting systematic glaucoma screening tests in patients with obstructive sleep apnea.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: <http://dx.doi.org/10.1016/j.sleep.2013.11.790>.

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